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RAWLINGS, STEPHEN L	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/649,591	MARKOWITZ, SANFORD D.	
	Examiner	Art Unit	
	Stephen L. Rawlings	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *75,84-91,93-102,104-106,123 and 124* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *75,84-91,93-102,104-106,123 and 124* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The amendment filed February 1, 2008, is acknowledged and has been entered. Claims 75, 91, 94, 99, 123, and 124 have been amended.

2. Claims 75, 84-91, 93-102, 104-106, 123, and 124 are pending in the application and are currently under prosecution.

Grounds of Objection and Rejection Withdrawn

3. Unless specifically reiterated below, Applicant's amendment and/or arguments have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed September 17, 2007.

Priority

4. Applicant's claim under 35 USC § 120 for benefit of the earlier filing date of the U.S. Patent Application No. 10/274,591, filed October 18, 2002, which claims benefit of U.S. Patent Application No. 10/299,345, filed August 26, 2002, is acknowledged.

However, none of claims 75, 84-91, 93-102, 104-106, 123, and 124 properly benefit under 35 U.S.C. § 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected herein under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure.

Again, to receive benefit of the earlier filing date under 35 USC § 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

In addition, as explained in the preceding Office action, claims 86 and 87 do not properly benefit under 35 U.S.C. § 120 by the earlier filing dates of the priority documents claimed because the prior filed applications do not describe the practice of the claimed invention using a biological sample derived from the inner wall and/or lumen of the intestinal tract, such as a stool sample removed from within the colon.

Therefore, at present, the effective filing date of claims 75, 84-91, 93-102, 104-106, 123,and 124 is deemed the filing date of the instant application, namely August 26, 2003.

Grounds of Objection and Rejection Maintained

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. The rejection of claims 75, 84-91, 93-102, 104-106, 123, and 124 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is maintained. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a "written description" rejection.

Beginning at page 10 of the amendment filed February 1, 2008, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Claims 75, 84-91, 93-102, 104-106, 123, and 124 are directed to a genus of secreted polypeptides having varying structures and no particular function.

For example, claim 75 is directed to a polypeptide having an amino acid sequence that is at least 95% identical to SEQ ID NO: 21. Although structurally related to a polypeptide having the amino acid sequence of SEQ ID NO: 21, the polypeptide to which the claims is directed need not have the same function as that of the former; moreover, it need not have any function at all.

As such, there is no correlation between any one particularly identifying structural feature, which is shared by members of the claimed genus of polypeptides, and any one particularly identifying functional feature, which is also shared by at least a substantial number of its members; consequently the skilled artisan could not immediately envision, recognize or distinguish members of the claimed genus. Therefore, the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Although the polypeptides to which the claims are directed are polypeptides present in samples acquired from subjects deemed likely to have a colon neoplasm, the patient likely to have a neoplasm does not have a neoplasm; therefore, even if one were to screen for the presence of such a polypeptide in samples acquired from a multitude of subjects, because it cannot be known which subjects are the subjects, if not all, which are likely to have a colon neoplasm, there is no way of establishing that any given polypeptide having the requisite structure in the sample is that to which the claims are directed, or not. In other words, before it can be established that the presence of a polypeptide having an amino acid sequence that is at least 95% identical to SEQ ID NO: 21, for example, is indicative of a sample acquired from a subject likely to have a colon neoplasm, it would first be necessary to know or determine which subjects are likely to have such a disease; but because it cannot be determined whether any patient is more or less likely to have a colon neoplasm than any other, or more precisely because the amount of guidance, direction and exemplification set forth in this application would not reasonably enable the artisan to do so, it would not be possible know or determine which polypeptides are those to which the claims are directed.

How are subjects likely to have a colon neoplasm identified? Presumably every subject having a colon is at some risk for developing a colon neoplasm. Is the invention

a process for determining the likelihood that a subject will later develop a colon neoplasm, or is it a process for establishing a probability that a subject now has such a disease?

How *likely* must the likelihood that a subject has a colon neoplasm be, in order to be considered a subject according to the claims (i.e., a subject comprised of cells, tissues or fluids, which are sampled and which upon analysis are determined to contain a secreted polypeptide having the requisite structure?

It is for such reasons that the polypeptide to which the claims are directed, and which is present in a biological sample acquired from a subject likely to have a colon neoplasm, so as to provide indication upon its detection of such likelihood, must be described with a level of clarity and particularity that would immediately permit the skilled artisan to envision, recognize or distinguish that polypeptide.

Applicant is reminded that "generalized language may not suffice if it does not convey the detailed identity of an invention." *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

In this instance, there is no language that adequately describes the members of the genus of secreted polypeptides that are detected in a biological sample acquired from a subject, so as to achieve the claimed objective. A description of what a material does, where it is found, or how it is used, *rather than of what it is*, does not suffice to describe the claimed invention.

"Regardless whether a compound is claimed *per se* or a method is claimed that entails the use of the compound, the inventor cannot lay claim to the subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods". *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1894 (CAFC 2004). It is submitted unlikely that every polypeptide having an amino acid sequence that is at least 95% identical to either SEQ ID NO: 21 or SEQ ID NO: 3 will be found to be expressed and then secreted only by neoplastic colon cells (e.g., colon cancer cells, colon adenoma cells), as opposed to normal colon cells. Thus, the claimed method depends upon finding the secreted polypeptides having the requisite structures that are

present in a biological sample acquired from a subject that is likely to have a colon neoplasm; without such polypeptides, it is impossible to practice the invention.

As previously explained, although the skilled artisan could potentially identify polypeptides similar to the polypeptide of SEQ ID NO: 21 that are present in samples acquired from subjects that are likely to have colon neoplasia, which might be used in practicing the claimed invention, it is duly noted that the written description provision of 35 U.S.C § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*.

Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (CAFC 1991). See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993); *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (CAFC 1991); *University of Rochester v. G.D. Searle Co.*, 69 USPQ2d 1886 1892 (CAFC 2004).

Moreover, absent the adequate description of a representative number of members of the genus of polypeptides to which the claims are directed, the supporting disclosure amounts to no more than a mere invitation to identify those other members of the claimed genus, which are not described with clarity and particularity in this application.

Neither the specific activities and/or biological functions of the polypeptides of SEQ ID NO: 3 and SEQ ID NO: 21, nor of any other secreted "ColoUp2" polypeptide that is encoded by a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 5, have been described in the specification.

Therefore, though the specification describes the polypeptide of SEQ ID NO: 3 and SEQ ID NO: 21 as members of the genus of secreted "ColoUp2" polypeptides to which the claims are directed, neither polypeptide is reasonably deemed representative of the genus, as a whole, because there is no disclosure of a structural feature shared

by each of member of the genus, including either of these particularly described polypeptides, which correlates with any common functional feature attributable to the shared structural feature. Again, the specific functions of the polypeptides to which the claims are directed is not known, or at least not disclosed in this application.

Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) states, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Because the claims encompass a genus of polypeptides, which vary both structurally and functionally, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. In this instance, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; Applicant has not shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; and Applicant has not described distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention at the time the application was filed.

As an additional point, the Federal Circuit has decided that a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. See *Noelle v. Lederman*, 69 USPQ2d 1508 1514 (CA FC 2004) (citing *Enzo Biochem II*, 323 F.3d at 965; *Regents*, 119 F.3d at 1568). As discussed in greater detail in the preceding Office action, there is in fact such unpredictability.

Due to their variable structures, members of the claimed genus of polypeptides are expected to have functions that differ substantially from that of the disclosed mature, secreted polypeptide of SEQ ID NO: 3. This position is supported, for example, by the teachings of Skolnick et al. (*Trends in Biotechnology* 2000; **18**: 34-39) (of record; cited by Applicant).

Therefore, the skilled artisan would not accept the assertion, which is based only upon an observed similarity in amino acid sequence, that a variant of the polypeptide of SEQ ID NO: 3, for example, is capable of functioning the same, or even as having the same structure as the polypeptide of SEQ ID NO: 3. If not sharing the same function, then why might it be reasonably expected that its presence in a biological sample acquired from a subject should provide an indication of the likelihood that the subject has colon cancer, perhaps? In general, genes that are differentially expressed in cancer cells are under- or over-expressed in those cells, as compared to normal cells of the corresponding cell and/or tissue types, for a reason. Usually the gene encodes a product that either retards the growth and/or progression of the cancer (e.g., a tumor suppressor gene), or it encodes a product that promotes growth and/or progression (e.g., an oncogene). If the presence of the polypeptide of SEQ ID NO: 3, for example, in a biological sample acquired from a subject is indicative of the presence of colon cancer in the subject, then it stands to reason that the polypeptide in some way or another is produced and/or secreted by the cancer cells because that polypeptide has a function that is directly or indirectly involved in the growth and/or progression of the cancer. If a variant of the polypeptide of SEQ ID NO: 3 lack this same function that plays some role in the etiology or pathology of colon cancer, then its mere presence in a biological sample should not be presumed indicative of the presence of colon cancer in the subject.

Even among closely related protein family members, the skilled artisan cannot predict whether a particular member of the family is associated with the etiology or pathology a specific disease, solely on the basis that another member of the family has been shown to be.

This position is supported, for example, by De Plaen et al. (*Immunogenetics.* 1994; **40**: 360-369) (of record; cited by Applicant). As previously explained, De Plaen et al. reviews the structure, chromosomal localization and expression of twelve genes encoding members of the MAGE family of proteins; see entire document (e.g., the abstract). De Plaen et al. teaches six of the members of the gene family were found to be expressed at a high level in a number of tumors of various histological types; while five were very weakly expressed in all samples tested, and one, namely MAGE 7, was not transcribed at all in the ninety-five tumor samples tested (page 367, column 1). Just as not all members of the MAGE family of proteins are associated with cancer, particularly, since is it not obvious what, if any, association the weakly expressed MAGE proteins have, it is apparent that the skilled artisan cannot predict, based upon the information disclosed in the specification, whether variants of the polypeptide of SEQ ID NO: 3, as members of a presumed family of structurally related proteins, have an association with the etiology or pathology of colon cancer (e.g., whether the genes encoding such variants are overexpressed in colon cancer).

Furthermore, just as some of members of the genus of polypeptides to which the claims are directed are not expected to have or retain the specific activities of the polypeptide of SEQ ID NO: 3, for example, it is also expected that at least some of the polypeptides to which the claims are directed are *not secreted* into the serum or other biological fluids of subjects afflicted with colon cancer; and as such, the presence of some of the polypeptides to which the claims are directed may not be indicative of the presence in the subject of a colon tumor.

Not all of the claims are generic. Claim 124 is directed to a polypeptide comprising the amino acid sequence of SEQ ID NO: 3. The amino acid sequence of SEQ ID NO: 3 is described as that of the mature, secreted form of a polypeptide, which is present in the serum of subjects afflicted by colon cancer; see, e.g., Figure 2; and paragraphs [0126] and [0127] of the published application[1].

[1] U.S. Patent Application No. 2006/0035237 A1.

Although this polypeptide is present in the media of CaCo2 colon cancer cells transfected with a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 5[2], *the presence of the polypeptide of SEQ ID NO: 3 in the serum or other bodily fluid obtained from a subject has not been correlated with the presence in the subject of a colon neoplasm*.

Instead, the specification merely shows that the gene encoding the polypeptide of SEQ ID NO: 14, which is described as the full-length (immature) polypeptide[3], is overexpressed in colon cancer and adenomas by an analysis of mRNA levels[4].

How or why would one be assured of the fact that colon cancer and adenoma cells that overexpress the gene encoding the polypeptide of SEQ ID NO: 14 will secrete the polypeptide of SEQ ID NO: 3?

It has been presumed that the polypeptide of SEQ ID NO: 14 is not secreted, despite its overexpression, since the specification describes the polypeptide of SEQ ID NO: 14 as a full-length polypeptide, and further discloses that it is post-translationally processed to yield the mature, secreted polypeptide of SEQ ID NO: 3.

Again, the specification discloses that the mature, secreted form of "ColoUp2" is present in the media of *transfected* CaCo2 colon cancer cells; but why was it necessary to transfect colon cancer cells with a nucleic acid molecule encoding the polypeptide to show that the cells are capable of secreting the polypeptide? If, as according to the claims, there is a correlation between the presence of the secreted polypeptide in a biological sample (e.g., the serum) acquired from a subject and the presence in the subject of colon cancer cells, are the cells not already expressing (and secreting) the polypeptide?

At page 13 of the amendment filed February 1, 2008, Applicant has remarked, "the specification also provides working examples to show that at least two secreted forms of ColoUp2 protein were successfully detected in the culture medium of cells and in the blood from a mouse bearing tumor xenografts" (paragraph 3).

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[2] See, e.g., paragraphs [0178] and [180] of the published application.
[3] See, e.g., paragraph [0143] of the published application.
[4] See, e.g., paragraphs [0159] and [0167].

In response, it is noted that the specification discloses, "we derived transfected cell lines that stably expressed and secreted V5-epitope tagged ColoUp1 and ColoUp2 proteins [and these] cells lines were then injected into athymic mice and grown as tumor xenografts". It was in these mice harboring cells transfected with a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 5, which had been previously shown to secrete a polypeptide comprising the amino acid sequence of SEQ ID NO: 3, that Applicant found in the bloodstream the secreted polypeptide encoded by the transgene contained in those cells.

The presence of the polypeptide in the serum of mice harboring the transfected cells should be no surprise, since the polypeptide was secreted by those same cells *in vitro*; but why would such a disclosure be reasonably argued to establish that the mere presence of the secreted polypeptide of SEQ ID NO: 3 in the serum of humans is indicative of the presence of a colon neoplasm?

There are notable differences in the scope of the claims and scope of such a disclosure.

For example, the cells were *transfected* with a nucleic acid molecule encoding the polypeptide that was found to be secreted; the secretion of the polypeptide by non-transfected colon cancer cells and/or colon adenoma cells has not been demonstrated. Yet, the claims are directed to a process for determining whether a subject is likely to a colon neoplasm, which is unlikely to be comprised of colon cancer cells expressing a transgene encoding one or both of the polypeptides to which the claims are directed.

The cells were either CoCa2 cells, Vaco400 cells, or SW480 cells. None of the cells were primary cells; none were derived from adenomas, and all were derived from colon cancer cells. Yet, the claims are directed to a process for determining whether a subject is likely to a colon *neoplasm*, not necessarily colon cancer.

Then, there is the apparent discrepancy as to which polypeptides are secreted by the transfected cells, which is further discussed in the paragraphs below.

According to claim 123, the polypeptide is a polypeptide comprising the amino acid sequence of SEQ ID NO: 21.

As previously noted, the specification incongruously discloses that the polypeptide of SEQ ID NO: 21 is structurally distinct from the polypeptide of SEQ ID NO: 3: "A peptide of sequence AVLAAHCPFYSWK was present only in the digest of the 55 KD fragment, but was absent from the digest of the full length protein, demonstrating that this peptide corresponded to the unique amino terminus of the 55 KD fragment" (paragraph [0180] of the published application)[5].

Nonetheless, the amino acid sequence of SEQ ID NO: 21 appears to be but a mere fragment of the amino acid sequence of the mature, secreted polypeptide (i.e., SEQ ID NO: 3)[6].

Although the specification discloses the presence of a 55 kDa "ColoUp2" polypeptide and a 85 kDa "ColoUp2" polypeptide in the culture media of CoCa2 colon cancer cells transfected with a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 5[7], it is not evident which, if either one of the secreted "ColoUp2" polypeptides, is a polypeptide consisting of the amino acid sequence of SEQ ID NO: 21.

The presence of the polypeptide of SEQ ID NO: 21 in the serum or other bodily fluid obtained from a subject has not been correlated with the presence in the subject of a colon neoplasm; and it is again noted that the specification only establishes that the gene is overexpressed in colon cancer and adenomas by an analysis of mRNA levels.

The polypeptide of SEQ ID NO: 21 comprises an amino acid sequence comprising a fragment of the amino acid sequence of SEQ ID NO: 3, but still differs from the polypeptide of SEQ ID NO: 3 by the inclusion in its amino acid sequence of a novel amino acid sequence; see, e.g., paragraph [0180] of the published application; and Figure 41.

Because of the disclosed structural differences between the polypeptide of SEQ ID NO: 3 and the polypeptide of SEQ ID NO: 21, there is a reasonable presumption that

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[5] This disclosure suggests the amino acid sequence of the disclosed 55 kDa polypeptide cannot be the amino acid sequence set forth as SEQ ID NO: 21.
[6] SEQ ID NO: 21 consists of the amino acid sequence set forth between the amino acids at positions 245-732, inclusive, of SEQ ID NO: 3.
[7] See, e.g., paragraphs [0178] and [180] of the published application.

the polypeptides have different activities and/or biologic functions, and the polypeptide of SEQ ID NO: 21 may not be secreted into the serum or other biological fluid by colon cancer cells, or any other type of cells.

As disclosed in the specification, molecular markers that occur in the urine are generally derived from a polypeptide that is present in the blood (paragraph [0099] of the published application); therefore, if the "ColoUp2" polypeptide is not secreted, it is not likely to be present in the blood or any fraction thereof. Notably, the specification further discloses that a molecular marker that is present in the lumen of the colon may be found in the intestinal mucous or in stool samples), provided the marker is secreted from the apical face of a cell (paragraph [0099] of the published application). So, if the "ColoUp2" polypeptide is not secreted from the apical face of the colon cell into the lumen, it may not be present in, for example, the stool of a subject.

The skilled artisan cannot predict whether the polypeptide of SEQ ID NO: 21, or any given variant of the polypeptides of SEQ ID NO: 3 and/or SEQ ID NO: 21 is secreted, and as so indicative of the presence in the subject of any precancerous or cancerous condition or disease in a subject.

Many of "ColoUp2" polypeptides to which the claims are directed may not be secreted; and then it is also expected that colon cells, as well as other types of cells, express and secrete at least some of these "ColoUp2" polypeptides. If so, then their presence alone in any given biological sample cannot provide an absolute indication of the presence of neoplastic colon cells in the subject, since it would instead provide an indication of the presence of these other types of cells that secrete the polypeptides.

As further explained in the following rejection of the claims, as failing to provide a sufficiently enabling disclosure to satisfy the requirement set forth under 35 U.S.C. § 112, first paragraph, this is indeed the case, since WO 2002/86443 A2, for example, teaches a polypeptide comprising the amino acid sequence of SEQ ID NO: 3 is secreted into the serum and other biological fluids by lung cancer cells; see entire document (e.g., pages 351 and 352). Similarly, WO 2002/102235 A2 teaches ovarian cancer cells secrete this same polypeptide; see entire document (e.g., pages 304 and 305).

Thus, the presence of a polypeptide comprising the amino acid sequence of SEQ ID NO: 3 in a sample acquired from a subject *alone* cannot indicate the presence in the subject of neoplastic colon cells, since it appears to instead be indicative of the presence in the subject of lung or ovarian cancer cells.

Then, as previously pointed out, the specification discloses that Applicant predicts that "ColoUp2" is likely secreted at least in part from the basolateral epithelial face, and hence should be detectable as a serologic marker of large colon adenomas; see paragraphs [0169] and [0178] of the published application). Yet, while perhaps the presence of secreted isoforms of the polypeptide of SEQ ID NO: 14 in the serum of subjects may ultimately be found to provide an indication that the subject has such large colon adenomas or adenocarcinomas, it is submitted that because of an evident lack of particularity the disclosure would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Indeed, the specification describes the presence of a transcript encoding the polypeptide of SEQ ID NO: 14 in premalignant colon adenomas, as well as in 90% of Dukes stage B (early node negative colon cancers), Dukes stage C (node positive colon cancer), Dukes stage D (primary colon cancers with associated metastatic spread) and in colon cancer liver metastasis, colon cancer cell lines, and in colon cancer xenografts grown in athymic mice (paragraphs [0167] of the published application). However, the specification only shows that *transfected* cell lines, which have been engineered to express a nucleic acid molecule encoding the full-length polypeptide of SEQ ID NO: 14, secrete the polypeptides of SEQ ID NO: 3 and/or SEQ ID NO: 21 (see, e.g., paragraph [0174], [0177], and [0178] of the published application); it fails to demonstrate the presence of either polypeptide in the blood, or a fraction thereof, urine, or stool of a subject known to have any precancerous or cancerous growth of the colon. Contrary to Applicant's assertion, the expression of the gene encoding the polypeptides of SEQ ID NO: 3 and/or SEQ ID NO: 21 may not yield detectable quantities of the polypeptides in the blood, urine, or stool because the specification has not disclosed that the amount of the polypeptide secreted by the cells is concordant with the amount of mRNA produced by the cell.

Again, it is well established one cannot predict whether the level of protein produced by a cell will reflect the amount of mRNA produced by the cell: "But having acknowledged that control of gene expression can occur at multiple stages, *and that production of RNA cannot inevitably be equated with production of protein*, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription" (italicized for emphasis) (Genes VI, 1997; Ed. Benjamin Lewin; Chapter 29, first page).

As further emphasized by the teachings of Chen et al. (*Molecular & Cellular Proteomics.* 2002; **1**: 304-313) (of record; cited by Applicant), one cannot merely presume that, because there is an association between the amount of mRNA produced by a given sample of cells and the presence of cancer, the amount of protein encoded by that mRNA may also associated with the presence of cancer in the sample. Chen et al. teaches expression of protein and mRNA in cancer are discordant; see entire document (e.g., the abstract). Liu et al. (*Cancer J.* 2001 Sep-Oct; **7** (5): 395-403) (of record; cited by Applicant) shows similarly that the amplification of the gene encoding HER-2, another tumor-associated antigen, which often leads to over-expression, does not necessarily correlate with over-expression. Liu et al. shows that amplification of the gene encoding HER-2 was detected in a substantial portion of prostate cancer cells that do not over-express the protein; see entire document (e.g., the abstract).

Given such facts, it is submitted that a demonstration that transfected xenografts artificially secreted detectable quantities of the polypeptides of SEQ ID NO: 3 and/or SEQ ID NO: 21 into the sera of mice, such as that presented in this application (paragraph [0174] of the published application) should not suffice to establish the presence of either polypeptide in a subject having or likely to have a colon neoplasm, such as a polyp, adenoma, or adenocarcinoma. Such a demonstration does not determine whether the amount of the polypeptide secreted into the blood, urine, or stool by the cells of such colon neoplasms in human subjects, for example, is concordant with the amount of mRNA produced by those cells.

Further support for this position is found, for example, in the teachings of Roessler et al. (*Mol. Cell. Prot.* 2006; **5** (11): 2092-2101) (of record). As previously

explained, Roessler et al. teaches that of five proteins identified as elevated in tissue samples obtained from individuals with colorectal cancer only one of these proteins could be shown to be elevated in serum samples obtained from individuals with colorectal cancer; see entire document (e.g., page 2099, right column). Additionally, Roessler et al. (*Clin. Can. Res.* 2005; **11** (18): 6550-6557) (of record) teaches, while proteins may be elevated in tissue samples obtained from individuals with colorectal cancer, "which of the cancer-associated proteins found in tumor tissue that eventually will be present in serum or plasma cannot be predicted *a priori*"; see entire document (e.g., page 6556, right column). Thus, according to Roessler et al., development of highly sensitive immunoassays for each candidate marker and subsequent assessment of serum/plasma samples is mandatory (page 6556, right column). Similarly, Zolg et al. (*Mol. Cell. Prot.* 2004; **3** (4): 345-354) (of record) discloses, upon commenting on whether proteins identified as elevated in cancer tissue screens will also be elevated in liquid samples obtained from individuals, "[an] inherent risk in the tissue approach is the fact that the candidate marker identified in e.g., tissue cannot later be detected in peripheral fluid such [as] serum"; see entire document (e.g. page 347, right column).

It is for all of the above reasons that it is submitted that the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention as of the time the application was filed, so as to satisfy the written description requirement set forth under 35 U.S.C. § 112, first paragraph.

Finally, it is noted that Applicant has requested reconsideration in view of *Ex parte Bandman*; see the remarks beginning at page 12, paragraph 2, of the amendment. Although that decision has been considered, Applicant is reminded that the Federal Circuit has repeatedly decided that each case involving the issue of written description, "must be decided on its own facts. Thus, the precedential value of cases in this area is extremely limited." *Vas-Cath*, 935 F.2d at 1562 (quoting *In re Driscoll*, 562 F.2d 1245, 1250 (C.C.P.A. 1977)). See *Noelle v. Lederman*, 69 USPQ2d 1508 (CA FC 2004).

7. The rejection of claims 75, 84-91, 93-102, 104-106, 123, and 124 under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for using** a processes comprising obtaining a biological sample (i.e., tissue, blood or a fraction thereof (e.g., serum or plasma), or stool) from a subject and determining the presence and/or amount of a secreted polypeptide comprising the amino acid sequence of SEQ ID NO: 3, **does not reasonably provide enablement for using** the claimed processes for determining whether a subject is likely to have a colon neoplasm, is maintained. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Beginning at page 13 of the amendment filed February 1, 2008, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

As explained in the "written description" rejection above, the claims are directed to a genus of secreted "ColoUp2" polypeptides, which differ both structurally and functionally. As further explained above, the skilled artisan cannot predict, based upon the information disclosed in the specification, whether secreted "variants" of the polypeptides of SEQ ID NO: 3 and SEQ ID NO: 21, even as members of a presumed family of structurally related proteins, have an association with the etiology or pathology of colon precancer and colon cancer. That is, for example, the skilled artisan cannot predict whether the genes encoding such secreted variants are overexpressed in colonic polyps, adenomas, or colon cancer, as compared to normal colon tissue, or whether the polypeptides encoded by these gene are secreted into the blood, urine, or stool of a subject afflicted by the condition or disease, so as to serve as biomarkers of the disease.

The specification describes that the presence of a secreted polypeptide(s) having the amino acid sequences of SEQ ID NO: 3 or SEQ ID NO: 21 in the conditioned medium used to culture transfected cells expressing nucleic acid molecules encoding these proteins; see, e.g., paragraph [0171] of the published application. Similarly, the specification describes the appearance of these polypeptide(s) in the serum of mice implanted with transfected xenograft tumor cells expressing the polypeptide(s); see, e.g., paragraph [0174] of the published application.

The specification, however, fails to demonstrate the presence of any one of the "ColoUp2" polypeptides (e.g., the polypeptide of SEQ ID NO: 3) in any biological sample, such as blood, urine, or stool acquired from subjects known to have a colonic polyp, a colon adenoma or a colon carcinoma; moreover, apart from the polypeptides of SEQ ID NO: 3 and SEQ ID NO: 21, it appears that the disclosure fails to describe with the requisite particularity any other "ColoUp2" polypeptide, which may serve as a plasma, serum, urine, or stool marker, for example, of such colon neoplasms.

At page 14 of the amendment filed February 1, 2008, Applicant has disagreed with the above remarks, arguing that the specification describes the presence of a polypeptide comprising SEQ ID NO: 3 in the serum of mice (i.e., "subjects").

In response, it seems doubtful that Applicant intends the invention be used to determine whether an experimental mouse that has been inoculated with a colon cancer cell line transfected with a nucleic acid molecule encoding a secreted polypeptide according to the claims is likely to have a colon neoplasm, since of course the mouse would be expected to develop just such disease.

The "subject" to whom the claims are directed is not necessarily a mouse; and although the specification defines the term "subject" in paragraph [0091] of the published to include a mouse, when one considers, for example, the disclosures at paragraphs [0003]-[0007] of the published application, it appears that the term is intended more often than not to refer to a human patient, not an experimental animal.

Then, as mentioned, although the specification describes an detecting the presence of the secreted polypeptide in the serum of mice inoculated with cancer cells expressing the protein, the claims are directed to a process for determining whether or

not a subject is likely to have a colon neoplasm – mice inoculated with cancer cells expressing the secreted protein are expected to have colon neoplasms, and the detection of the secreted protein in the sera of the mice would only serve to confirm that the protein is secreted by those cells *in vivo*, as well as when cultured *in vitro*.

Nonetheless, if Applicant were to amend the claims, such that the claims were specifically directed to a subject that is a mouse inoculated with cancer cells expressing the transgene encoding the secreted polypeptide, the Examiner supposes that the specification would be rightly deemed enabling of the use of the claimed process.

If not, then, the Examiner disagrees with Applicant's assertion that the use of the claimed invention has been demonstrated, since the specification does not demonstrate the presence of the polypeptide of SEQ ID NO: 3 or SEQ ID NO: 21 in blood, or a fraction thereof, urine, or stool of a subject (e.g., a human patient) known to have a benign, precancerous, or cancerous neoplastic growth of colon cells or tissue.

Certainly one would not practice the claimed invention by inoculating a human patient with cancer cells expressing the transgene encoding the secreted polypeptide, as Applicant has demonstrated using a mouse – rather the invention would be practiced, as suggested, namely to determine whether or not a subject has or is likely to have such a neoplastic growth, which in the "real-world" might facilitate, for example, an early diagnosis of the disease and more effective treatment thereof.

Again, considering the vastly different structures and functions of the members of the genus of polypeptides to which claims are directed, it is reasonably expected that the presence in a biological sample of most of the polypeptides to which the claims are specifically directed would not provide an indication of the presence of such a condition or disease, or of the likelihood that the subject has such a condition or disease, since, for example, many of the polypeptides may not be expressed in the normal colon or even in colon cancer cells. Thus, any success in practicing of the claimed invention by determining the presence of any polypeptide other than the polypeptides of SEQ ID NO: 3 and/or SEQ ID NO: 21 is most unpredictable, but because the specification fails to establish the presence of the polypeptides of SEQ ID NO: 3 and/or SEQ ID NO: 21 in the blood, urine or stool of a subject having or likely to have a colonic polyp, adenoma,

or carcinoma, it is submitted that the skilled artisan could not practice any one embodiment of the claimed invention without undue and/or unreasonable experimentation. Before the skilled artisan might reasonably be capable of using the claimed process to achieve the claimed objective (i.e., the determination that a subject has or is likely to have a colon neoplasm), it would be necessary to determine if the "ColoUp2" polypeptide (e.g., the polypeptide of SEQ ID NO: 3) is actually secreted into the blood of a subject known to have such a colon neoplasm, and then whether or not its presence in the blood, urine, or stool of the subject is indicative of the presence in the subject of the colon neoplasm, as opposed to, for example, the presence of some other normal or abnormal cell type that also expresses the polypeptide. Even then, it would still be necessary to identify other secreted polypeptides that are produced by the expression of a nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 5 (e.g., other isoforms encoded by splice variants of the mRNA encoding the polypeptides of SEQ ID NO: 14, SEQ ID NO: 3 and/or SEQ ID NO: 21), which are suitable markers for colon neoplasms, and then it would be necessary to elaborate the processes for detecting the presence of such neoplasms in a biological sample that involves the detection of those other polypeptides.

Given, in particular, the degree to which the members of the "ColoUp2" polypeptides may vary, both structurally and functionally, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify a secreted "ColoUp2" polypeptide present in a biological sample of a subject having or likely to have a colon neoplasm, which might serve as a biomarker of that condition or disease.

Applicant is reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the

invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

The molecular detection and diagnosis of cancer, or the molecular assessment of a subject's risk for (i.e., the likelihood of) developing cancer is a highly unpredictable art, because of the complexities of the biological systems and the many and variable mechanisms by which cancer forms and progresses. In the absence of scientific and clinical validation of the utility of a putative biomarker, such as the polypeptide of SEQ ID NO: 3, the skilled artisan could not use the claimed invention to detect the presence of a precancerous or cancerous neoplasm of the colon, or to assess a subject's risk for developing such a condition or disease.

The teachings of Rae et al. (*International Journal of Cancer.* 2000; **88**: 726-732), for example, emphasizes the need to validate initial studies suggesting that a gene encoding a tumor marker is overexpressed in carefully controlled studies using "matched" (i.e., acquired from the same subject) normal control specimens. Rae et al. teaches a highly sensitive method for determining the differential expression of genes associated with cancer; see entire document (e.g., the abstract). A total of sixteen tumor and sixteen adjacent normal tissue samples were collected at the same time from the patients. The tumor tissue was histologically confirmed to be clear-cell renal cell carcinoma (RCC); and the tumors were staged by a conventional system. Rae et al. discloses that using differential display PCR, it was determined that some genes were identified that were expressed at higher levels in the tumor specimens than in the normal specimens, while other genes were expressed at lower levels in the tumor specimens. Notably, Rae et al. had planned to use as a positive control, primers that amplify a complementary DNA (cDNA) molecule encoding "DD96", a gene that had been previously reported by Kocher et al. to be up regulated in RCC. However, Rae et al. found that in contrast to the results reported by Kocher, et al, no *consistent* up- or down-regulation of *DD96* was evident when using either RT-PCR or Northern analysis. Rae et al. concludes, "we do not believe that *DD96* up-regulation is highly associated with RCC, particularly in early progression, and does not warrant extensive further investigation in the context of this disease" (page 731, column 2). Rae et al. suggests

that the results of Kocher et al. were inaccurate because their experiments were not properly controlled. In contrast to the study of Kocher et al., Rae et al. discloses, "only those cDNAs clearly up- or down-regulated in duplicate paired RCC and normal kidney samples (Fig. 1) from 4 different patients were considered to be definitively differentially expressed" (page 728, column 1). Moreover, their results were considered accurate only when the cDNAs were successfully re-amplified and only when no expression was detected in the paired (i.e., matched) sample. Thus, while the specification may disclose data that is suggestive that a nucleic acid encoding the polypeptide of SEQ ID NO: 14, and presumably the secreted isoforms thereof comprising the amino acid sequences of SEQ ID NO: 3 and/or SEQ ID NO: 21, is present in relatively greater abundance in colon adenoma cells and colon cancer cells, as compared to normal colon cells, because the data was not apparently acquired using appropriately matched controls as references, it is submitted that the results would have to be verified before it would be prudent to determine if the presence of the protein in any given biological sample acquired from a subject, such as blood or urine, is indicative of the presence in the subject of a colon neoplasm.

Notably, even in instances where carefully controlled experiments establish the that a biomarker is differentially expressed by cancer cells, compared to matched normal cells of the same tissue, the determination of the presence or expression of some tumor markers has proven to be ineffective in enabling an accurate and reliable diagnosis of all stages of cancer. Ward (*Developmental Oncology* 1985; **21**: 91-106) teaches not all markers can be reliably used in primary diagnosis; see, e.g., pages 96 and 97. Ward teaches that a number of tumor-associated markers are, in fact, diagnostically unreliable. Rather, Ward teaches some markers are more useful as guides in monitoring the efficacy of treatment modules for malignant disease; see, e.g., pages 98 and 99.

Critchfield (*Disease Markers* 1999; **15**: 108-111) teaches: "Indeed, to truly benefit society, the clinical value of the gene must be established" (page 109, column 1). Following the discovery of a novel gene, Critchfield discloses the process of determining whether the gene can be used successfully as a biomarker for diagnosis is

lengthy and involved. Similarly, the discovery of a possible association between the expression of a gene and cancer would be followed by an equally long and arduous process by which it is determined if the over- or under-expression of the gene in cancer cells, relative to its normal level of expression in normal cells, can be used to diagnose or detect cancer. Sidransky (*Science* 1997; **278**: 1054-1058) teaches this process must first establish the reliability of a novel diagnostic method, which measures the expression of a biomarker, through feasibility studies; then, after the reliability of the technique is established, its sensitivity and specificity must be assessed in formal clinical trials before the technique can be used with a reasonable expectation of success (page 1055, columns 1 and 2). Tockman et al. (*Cancer Research* 1992; **52**: 2711s-2718s) teaches considerations necessary in bringing a cancer biomarker (intermediate endpoint marker) to successful clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to risk assessment, diagnosis, and/or prognosis of any type of cancer. Tockman et al. teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence, and confirm marker predictive value in prospective population trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and if validated can be used for population screening (page 2713, column 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and link those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate endpoint marker (page 2714, column 1). Clearly, prior to the successful application of newly described markers, these must be validated against acknowledged disease end points; and, the marker

predictive value must be confirmed in prospective population trials (page 2716, column 2).

In this instance, there is considerable evidence that the claimed process could not be used to achieve the claimed objective of determining whether a subject has or is likely to have a colon neoplasm, particularly if the biological sample is not of the colon, but is instead a sample of the subject's blood, urine, or stool. WO 2002/102235 A2 (Mack et al.) teaches a polypeptide comprising an amino acid sequence that is identical to the amino acid sequence set forth as SEQ ID NO: 3; but Mack et al. teaches the polypeptide is overexpressed in ovarian cancer. Thus, the presence of the polypeptide comprising the amino acid sequence of SEQ ID NO: 3 in the serum of a subject is not necessarily indicative of the presence in the subject of a colon neoplasm, since it is instead just as likely due to the presence in the subject of ovarian cancer. Similarly, WO 2002/86443 A2 (Aziz et al.) teaches a polypeptide comprising an amino acid sequence that is identical to the amino acid sequence set forth as SEQ ID NO: 3; but Aziz et al. teaches the polypeptide is overexpressed in lung cancer. Thus, it is again apparent that the presence of the polypeptide comprising the amino acid sequence of SEQ ID NO: 3 in the serum of a subject is not necessarily indicative of the presence in the subject of a colon neoplasm, but may instead just as likely be due to the presence in the subject of lung cancer, if not ovarian cancer.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enable the skilled artisan to use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Notably Applicant has provided an exhibit, marked "Exhibit A", which Applicant has remarked shows successful detection of "ColoUp2 polypeptides" in biological samples (e.g., serum) acquired from colon cancer patients.

Which biological samples were used in the analyses? Serum, or some other sample?

Which "ColoUp2 polypeptides" were present in these samples? The polypeptide of SEQ ID NO: 3, the polypeptide of SEQ ID NO: 21, or both? How was the presence of these polypeptides in the serum detected? What reagents were used?

Applicant has further remarked that the results show that following surgical removal of the colon cancer, the level of circulating "ColoUp2" fell in all patients.

Which data represent such results? To which of the "ColoUp2 polypeptides" is this remark referring?

Applicant has remarked that the data points above the line represent samples acquired from patients in which the circulating level of CEA fell more than the circulating level of "ColoUp2" following surgery, whereas data points below the line represent samples acquired from patients in which the circulating level of "ColoUp2" fell more than the circulating level of CEA following surgery. Because there are a greater number of data points below the line, Applicant has asserted that the data indicate that "ColoUp2" is the better marker.

Although it is less than clear how or why such a conclusion might have been reached, it is submitted that the data does not establish a correlation between the presence of the polypeptide of SEQ ID NO: 3 or SEQ ID NO: 21 in a biological sample acquired from a subject and the likelihood that the subject has a colon neoplasm. If the subject has had surgery and the cancer has been resected, the subject should no longer have a colon neoplasm; so then how does data showing that "ColoUp2" is a better marker than CEA because its level drops more rapidly after surgery show that the invention can be used as claimed to determine the likelihood that the subject has a colon neoplasm?

Certainly if the tumor was resected, and a detectable level of "ColoUp2" remains in the patient's serum, the invention cannot be used, as claimed, because the practitioner of the claimed invention would wrongly conclude, based upon the presence of the polypeptide in a sample of the patient's serum, that the patient is likely to have a colon neoplasm, when he or she should not. The tumor was removed by the surgery;

and the thus the likelihood that that subject has a colon neoplasm should be close to none.

Finally, regardless of any possible merit of the data presented in Exhibit A, Applicant is reminded that such supporting documents cannot be relied upon to correct the deficiencies of the specification by supplying the necessary and essential teachings, guidance, and exemplification that the specification lacks. See M.P.E.P. § 2164.05(a). Therefore, even if it is Applicant's position that the data in Exhibit A establish that the claimed invention can be used to achieve the claimed objective, it is the Office's position that the specification, as filed, would not have reasonably enabled its use without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

9. The rejection of claims 75, 84-87, 89-91, 93-98, 100-102, 104-106, 123, and 124 nder 35 U.S.C. 102(e), as being anticipated by U.S. Patent Application Publication No. 2004/0005563 A1 (of record; cited by Applicant), is maintained.

Beginning at page 15 of the amendment filed February 1, 2008, Applicant has traversed the propriety of maintaining this ground of rejection, arguing that the prior art teaches the process is used to diagnose and/or treat ovarian cancer, not a colon neoplasm.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

The claims are directed to processes comprising obtaining a biological sample (i.e., tissue, blood or a fraction thereof (e.g., serum or plasma), or stool) from a subject and determining the presence and/or amount of a secreted polypeptide comprising the amino acid sequence of SEQ ID NO: 3.

U.S. Patent Application Publication No. 2004/0005563 A1 (Mack et al.) teaches a process comprising obtaining a biological sample from a subject and detecting in the biological sample the presence and/or amount of a secreted polypeptide comprising the amino acid sequence of SEQ ID NO: 87, which is identical to the amino acid sequence of SEQ ID NO: 3, as disclosed in this application, and comprises the amino acid sequence of SEQ ID NO: 21, also as disclosed in this application; see entire document (e.g., paragraphs [0213], [0216], [0217], [0220], [0222], and [0241]). Mack et al. teaches the biological sample obtained from the individual is a sample of blood or a fraction thereof (i.e., plasma or serum), or stool; see, e.g., paragraphs [0061], [0140], and [0220]. Mack et al. teaches the presence and/or amount the polypeptide in the biological sample is determined by an immunoassay that employs an antibody that binds to the polypeptide, such as immunoprecipitations, Western blot analyses, and/or ELISAs; see, e.g., paragraphs [0220] and [0264]. Accordingly, Mack et al. teaches the antibody is detectably labeled with a detectable substance, such as an enzyme, fluorescent substance, chemiluminescent substance, a chromophore, a radioactive isotope, or a complexing agent (e.g., a detectably labeled secondary antibody); see, e.g., paragraphs [0218]-[0220] and [0264]. Mack et al. teaches the process comprises determining the amount of the polypeptide in a biological sample obtained from a normal subject and comparing the values of the amounts of the polypeptides in the different samples; see, e.g., paragraphs [0041], [0111], and [0349]. Mack et al. teaches the process aids in determining therapeutic protocols; see, e.g., paragraphs [0105] and [0106].

In addition, Mack et al. does not teach that the subject is previously diagnosed with any disease, such as cancer; so, it follows that the process disclosed by Mack et al.

is practiced using a subject according to claim 102, namely a subject not previously diagnosed with colon cancer.

In response to Applicant's argument, though Applicant intends the process is used to determine whether a subject is likely to have a colon neoplasm, the active process taught by the prior art is materially and manipulatively indistinguishable from that of the claimed process.

Notably, the subject to which the claims are directed need not have a colon neoplasm; and the sample need not comprise the secreted polypeptide. Accordingly, the claims would not be infringed *only* in those instances wherein the subject is determined to have a colon neoplasm, as it would be infringed if the result were negative; and presumably it is not with such a limitation that Applicant intends to claim that process.

Furthermore, if, as Applicant has argued the prior art teaches the process is used to diagnose ovarian cancer, as opposed to a colon neoplasm, is the objective of the claimed invention not met in practicing the process as disclosed by the prior art, where the result is a determination that the subject has ovarian cancer? In other words, if it is determined that a biological sample from a subject comprises an amount of a secreted polypeptide comprising the amino acid sequence of SEQ ID NO: 3, and it is concluded upon the basis of this result that the subject has ovarian cancer, then is that subject not *unlikely* to have a colon neoplasm?

10. The rejection of claims 75, 84, 85-87, 89-91, 93-98, 100-102, and 104-106 under 35 U.S.C. 102(a), as being anticipated by WO 2002/068677 A1 (of record; cited by Applicant), is maintained.

Beginning at page 16 of the amendment filed February 1, 2008, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

The claims are directed to processes comprising obtaining a biological sample (i.e., tissue, blood or a fraction thereof (e.g., serum or plasma), or stool) from a subject

and determining the presence and/or amount of a secreted polypeptide comprising an amino acid sequence that is at least 95% identical to SEQ ID NO: 3 or SEQ ID NO: 21.

WO 2002/268677 A1 (Mack et al.) teaches a secreted polypeptide comprising an amino acid sequence that is at least 95% identical to the amino acid sequence of SEQ ID NO: 3 or SEQ ID NO: 21; see entire document (e.g., page 249, SEQ ID NO: 23; and Table 25 at page 238; and Table 21 at page 221). Mack et al. teaches the gene encoding this polypeptide is up-regulated in colon cancer, as compared to its level of expression in normal colon tissue; see, e.g., Table 21 at page 221. Mack et al. teaches detecting colon cancer in a subject by acquiring a biological sample (e.g., a sample of blood, serum, or stool) and determining if the secreted polypeptide is present in the sample using an immunoassay that employs a labeled or unlabeled antibody that binds to the polypeptide; see, e.g., pages 3, 5, 22, 23, 32, 33, 45-50, 52 and 53. Mack et al. teaches the process comprises quantifying the level of expression by measuring the amount of the polypeptide in the sample; see, e.g., page 51. Mack et al. teaches the immunoassay is an assay involving a Western blot, an immunoprecipitation assay, a radioimmunoassay, or an ELISA; see, e.g., page 53. Mack et al. teaches the antibody that is used in such assays, when labeled, is labeled using an enzyme, radioactive moiety, chromophore, or fluorescent or chemiluminescent substance; see, e.g., pages 15, 16, and 53. Mack et al. teaches the subject has either not been previously diagnosed or is currently receiving therapy for colon cancer; see, e.g.; page 3. Mack et al. teaches the process detects metastatic colon cancer, as well as precancerous or benign conditions, such as colon adenoma; see, e.g., pages 5 and 8. Mack et al. teaches the process comprises determining the amount of the polypeptide in a biological sample obtained from a normal subject and comparing the values of the amounts of the polypeptides in the different samples; see, e.g., Table 21 at page 221. Mack et al. teaches the detection of the presence of the polypeptide in a biological sample aids in the determining the therapeutic protocol to be administered to a subject having colon cancer; see, e.g., pages 2-8.

Applicant has argued that Mack et al. is not prior art under § 102(a).

In response, as explained above, none of claims 75, 84, 85-87, 89-91, 93-98, 100-102, and 104-106 properly benefit under 35 U.S.C. § 120 by the earlier filing dates of the priority documents claimed, *since those claims are rejected herein under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure*.

Again, to receive benefit of the earlier filing date under 35 USC § 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

In addition, as also explained, claims 86 and 87 do not properly benefit under 35 U.S.C. § 120 by the earlier filing dates of the priority documents claimed because the prior filed applications do not describe the practice of the claimed invention using a biological sample derived from the inner wall and/or lumen of the intestinal tract, such as a stool sample removed from within the colon.

Therefore, at present, the effective filing date of claims 75, 84, 85-87, 89-91, 93-98, 100-102, and 104-106 is deemed the filing date of the instant application, namely August 26, 2003; and for this reason, Mack et al. is prior art under § 102(a), since Mack et al. was published September 6, 2002.

Applicant has noted that another rejection of claims under §102(a), as being anticipated by Mack et al., was withdrawn, because Mack et al. was not prior art under § 102(a).

Applicant is reminded that each claim might have a different effective filing date; and if Applicant amends a claim, such that the amended claim is then rejected under § 112, first paragraph, that claim would not benefit from the earlier filing date of related applications. As a consequence, art that would not have originally been applied might then be applied, or re-applied.

Applicant has further argued that the prior art does not teach which genes are differentially expressed in colon cancer cells, as compared to normal colon cells.

In response, the claims are directed to processes comprising obtaining a biological sample (i.e., tissue, blood or a fraction thereof (e.g., serum or plasma), or stool) from a subject and determining the presence and/or amount of a secreted polypeptide comprising the amino acid sequence of SEQ ID NO: 3.

Mack et al. teaches the gene encoding a secreted polypeptide comprising an amino acid sequence that is identical to the amino acid sequence of SEQ ID NO: 3, and which comprises the amino acid sequence of SEQ ID NO: 21, is up-regulated in colon cancer, as compared to its level of expression in normal colon tissue; see, e.g., Table 21 at page 221. Mack et al. teaches detecting colon cancer in a subject by acquiring a biological sample (e.g., a sample of blood, serum, or stool) and determining if the secreted polypeptide is present in the sample using an immunoassay that employs a labeled or unlabeled antibody that binds to the polypeptide; see, e.g., pages 3, 5, 22, 23, 32, 33, 45-50, 52 and 53. Mack et al. teaches the process comprises quantifying the level of expression by measuring the amount of the polypeptide in the sample; see, e.g., page 51.

Applicant has argued that Mack et al. does not disclose "SEQ ID NO: 3".

In reply, the claims are directed to a secreted polypeptide comprising an amino acid sequence that is at least 95% identical to SEQ ID NO: 3 or SEQ ID NO: 21.

Mack et al. teaches a secreted polypeptide comprising an amino acid sequence that is at least 95% identical to SEQ ID NO: 3 and SEQ ID NO: 21.

11. The rejection of claims 75, 84-87, 89-91, 93-102, 104-106, 123, and 124 are rejected under 35 U.S.C. 102(a), as being anticipated by WO 2002/86443 A2, is maintained.

Beginning at page 18 of the amendment filed February 1, 2008, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

The claims are directed to processes comprising obtaining a biological sample (i.e., tissue, blood or a fraction thereof (e.g., serum or plasma), or stool) from a subject and determining the presence and/or amount of a secreted polypeptide comprising the amino acid sequence of SEQ ID NO: 3.

WO 2002/86443 A2 (Aziz et al.) teaches a process comprising obtaining a biological sample from a subject and detecting in the biological sample the presence and/or amount of a secreted polypeptide comprising the amino acid sequence of SEQ ID NO: 87, which is identical to the amino acid sequence of SEQ ID NO: 3, as disclosed in this application, and comprises the amino acid sequence of SEQ ID NO: 21, also as disclosed in this application; see entire document (e.g., page 5, lines 31-33; page 8, lines 9-19; page 34, lines 7-9; pages 351 and 352, SEQ ID NOs: 444 and 445). Aziz et al. teaches the biological sample obtained from the individual is a sample of blood or a fraction thereof (i.e., plasma or serum), or stool; see, e.g., page 9, lines 15-25. Aziz et al. teaches the presence and/or amount the polypeptide in the biological sample is determined by an immunoassay that employs an antibody that binds to the polypeptide, such as immunoprecipitations, Western blot analyses, and/or ELISAs; see, e.g., page 49, lines 26 and 27; and page 53, line 14, through page 54, line 20. Accordingly, Mack et al. teaches the antibody is detectably labeled with a detectable substance, such as an enzyme, fluorescent substance, chemiluminescent substance, a chromophore, a radioactive isotope, or a complexing agent (e.g., a detectably labeled secondary antibody); see, e.g., page 16, lines 11-21. Aziz et al. teaches the process comprises determining the amount of the polypeptide in a biological sample obtained from a normal subject and comparing the values of the amounts of the polypeptides in the different samples; see, e.g., page 4, lines 28-31; and Tables 1-16, beginning at page 83. Aziz et al. teaches the comparison is made using the values of the amounts of the polypeptide in sample acquired at multiple time points (e.g., using a sample obtained from the patient in past, as well as the present); see, page 4, lines 28-31; and page 9, lines 26-31. Aziz et al. teaches the process aids in determining therapeutic protocols; see, e.g., page 54, line 24, through page 55, line 4.

In addition, Aziz et al. does not teach that the subject is previously diagnosed with any disease, such as cancer; so, it follows that the process disclosed by Aziz et al. is practiced using a subject according to claim 102, namely a subject not previously diagnosed with colon cancer.

Applicant has argued that Aziz et al. is not prior art under § 102(a).

In response, as explained above, none of claims 75, 84, 85-87, 89-91, 93-98, 100-102, 104-106, 123, and 124 properly benefit under 35 U.S.C. § 120 by the earlier filing dates of the priority documents claimed, *since those claims are rejected herein under 35 U.S.C. § 112, first paragraph, as lacking adequate written description and a sufficiently enabling disclosure*.

Again, to receive benefit of the earlier filing date under 35 USC § 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

In addition, as also explained, claims 86 and 87 do not properly benefit under 35 U.S.C. § 120 by the earlier filing dates of the priority documents claimed because the prior filed applications do not describe the practice of the claimed invention using a biological sample derived from the inner wall and/or lumen of the intestinal tract, such as a stool sample removed from within the colon.

Therefore, at present, the effective filing date of claims 75, 84, 85-87, 89-91, 93-98, 100-102, 104-106, 123, and 124 is deemed the filing date of the instant application, namely August 26, 2003; and for this reason, Aziz et al. is prior art under § 102(a), since Aziz et al. was published October 31, 2002.

In addition, Applicant has argued that the prior art does not teach that the process is used to diagnose a colon neoplasm.

In response, though Applicant intends the process is used to determine whether a subject is likely to have a colon neoplasm, the active process taught by the prior art is materially and manipulatively indistinguishable from that of the claimed process.

Notably, the subject to which the claims are directed need not have a colon neoplasm; and the sample need not comprise the secreted polypeptide. Accordingly, the claims would not be infringed *only* in those instances wherein the subject is determined to have a colon neoplasm, as it would be infringed if the result were negative; and presumably it is not with such a limitation that Applicant intends to claim that process.

Furthermore, if, as Applicant has argued the prior art teaches the process is used to diagnose lung cancer, as opposed to a colon neoplasm, is the objective of the claimed invention not met in practicing the process as disclosed by the prior art, where the result is a determination that the subject has lung cancer? In other words, if it is determined that a biological sample from a subject comprises an amount of a secreted polypeptide comprising the amino acid sequence of SEQ ID NO: 3, and it is concluded upon the basis of this result that the subject has lung cancer, then is that subject not *unlikely* to have a colon neoplasm?

Lastly, Applicant has argued that the prior art does not teach a secreted polypeptide comprising the amino acid sequence of SEQ ID NO: 3.

In reply, Aziz et al. teaches a secreted polypeptide comprising the amino acid sequence of SEQ ID NO: 445, which is identical to the amino acid sequence of SEQ ID NO: 3, as disclosed in this application, and comprises the amino acid sequence of SEQ ID NO: 21, also as disclosed in this application; see entire document (e.g., page 5, lines 31-33; page 8, lines 9-19; page 34, lines 7-9; pages 351 and 352, SEQ ID NOs: 444 and 445). See GENSEQ database accession number ABU56623.

Conclusion

12. No claim is allowed.

13. As previously noted, the prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. WO 2002/30268 A2 (Gish et al.) (of record; cited by Applicant) teaches a secreted polypeptide comprising an amino acid sequence that is nearly identical to SEQ ID NO: 3, which is present in the serum of patients afflicted by prostate cancer.

14. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephen L. Rawlings/
Stephen L. Rawlings, Ph.D.
Primary Examiner, Art Unit 1643

slr
March 4, 2008